Guidance for Industry

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products

Chemistry, Manufacturing, and Controls Documentation

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Guirag Poochikian, Ph.D., (301) 827-1050.

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CMC

f. Net Content (Fill) Weight

The total net weight of all formulation components in the container should be determined. The net content weight of each of ten test containers should be in accordance with the release specification. For a description of this test, refer to the procedure for aerosols given in USP Chapter <755> Minimum Fill.

g. Drug Content (Assay)

The concentration of drug substance in the entire container should be determined analytically with a stability indicating method. The acceptance criteria should be tight enough to ensure conformance in other related attributes (e.g., dose content uniformity). Although this test may not be directly relevant in terms of performance of inhalation aerosols, it provides assurance of consistency concerning the manufacture of the drug product (e.g., formulation, filling, crimping, and sealing).

h. Impurities and Degradation Products

The levels of degradation products and impurities should be determined by means of stability indicating methods. Acceptance criteria should be set for individual and total degradation products and impurities. For identification and qualification thresholds, refer to the appropriate guidance. Individual impurities or degradation products appearing at levels 0.10 percent or greater should be specified. Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification.

FOR MDIs →

i. Dose Content Uniformity

Because of the complexity of the discharged dose, the medication available at the mouthpiece of the actuator should be thoroughly analyzed for an individual container, among containers, and among batches. This test may be regarded as providing an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, the valve, and the actuator. The number of actuations per determination should not exceed the number of actuations in the minimum dose approved in the labeling. A stability indicating method should be used. The amount of drug substance discharged should be expressed both as the actual amount and as a percent of label claim from the actuator. The USP Unit Spray <601> sampling apparatus may be used. This test is designed to demonstrate the uniformity of medication per actuation or dose, consistent with the label claim, discharged from the mouthpiece of a sample of an appropriate number of

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containers from a batch (n = 10 is recommended) . The primary purpose is to ensure dose uniformity within discharges from multiple containers of a batch. The following acceptance criteria are recommended:

- The amount of active ingredient per determination is not outside of 80–120 percent of label claim for more than one of ten containers, none of the determinations is outside of 75–125 percent of the label claim, and the mean is not outside of 85–115 percent of label claim. If two or three of the ten determinations are outside of 80–120 percent of the label claim, none is outside of 75–125 percent of label claim, and the mean is not outside of 85–115 percent of label claim, an additional 20 containers should be sampled (second tier). For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 80–120 percent of the label claim for more than 3 of all 30 determinations, none of the 30 determinations is outside of 75–125 percent of label claim, and the mean is within 85–115 percent of label claim.

j. Dose Content Uniformity Through Container Life

→ FOR MDI

The purpose of this test is to assess whether the product delivers the labeled number of full medication doses throughout the life of the MDI unit, and ensure that there is dose content uniformity for discharges within the same container. This test involves determining the dose content uniformity at the beginning of unit life, at the actuations corresponding to 50 percent of the fill weight (which may correspond to greater than 50 percent relative to the labeled number of actuations depending on overfill), and at the label claim number of actuations per container for an appropriate number of containers (n = 3 is recommended). The number of actuations per determination should not exceed the number of actuations in the minimum dose approved in the labeling. The rate of discharging between determinations should be such that it does not create excessive chilling of the MDI unit. The following acceptance critieria are recommended:

- The amount of active ingredient per determination is not outside of 80–120 percent of label claim for more than one of nine determinations from three containers, none of the determinations is outside of 75–125 percent of the label claim, and means for each of the beginning, middle, and end determinations are not outside of 85–115 percent of label claim. If two or three of the nine determinations are outside of 80–120 percent of the label claim, none is outside of 75–125 percent of label claim, and the

means for each of the beginning, middle, and end determinations are not outside of 85–115 percent of label claim, an additional six containers should be sampled at the beginning, middle and end of the canister (second tier). For the second tier of testing of a batch, the amount of active ingredient per determination is not outside of 80–120 percent of the label claim for more than 3 of all 27 determinations, none of the 27 determinations is outside of 75–125 percent of label claim, and the means for each of the beginning, middle, and end determinations are not outside of 85–115 percent of label claim.

k. Particle Size Distribution

One form of control which is more critical for inhalation aerosols than for most other conventional drug products is particle size distribution of the delivered dose. This parameter is dependent on the formulation, the valve, and the mouthpiece. The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1–5 microns.

From a pharmaceutical viewpoint, the most important parameter for an inhalation product is usually the aerodynamic particle size distribution of the outgoing aerosol. The aerodynamic particle size distribution is influenced by the characteristics of the spray of the drug product, as well as other factors, and is not solely determined by the size of the individual drug substance particles initially suspended in the formulation.

A multistage cascade impactor fractionates and collects particles of one or more drug components by aerodynamic diameter through serial multistage impactions. Such a device with all associated accessories should allow determination of a size distribution throughout the whole dose including, in particular, the small particle size fraction of the dose. It also provides information that allows for the complete mass balance of the total labeled dose to be determined. However, to minimize distortions and to ensure reproducibility, it is important to specify certain conditions such as information on the calibration of the equipment, flow rate, duration, the size and shape of the expansion chamber, or inlet stem, the selection of impaction surfaces, and the method, accessories, and adapters by which the inhalation aerosol is introduced into a specified impactor. These important parameters should be selected to obtain a complete profile of the dose. The rationale and documentation for selection of the above parameters should be presented. Additionally, criteria should be provided in the application for the qualification of each cascade impactor. It is recommended that all cascade